Thiophene Systems. 5. Thieno[3,4-*b*][1,5]benzoxazepines, Thieno[3,4-*b*][1,5]benzothiazepines, and Thieno[3,4-*b*][1,4]benzodiazepines as Potential Central Nervous System Agents[1]

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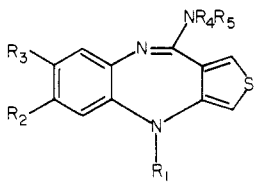
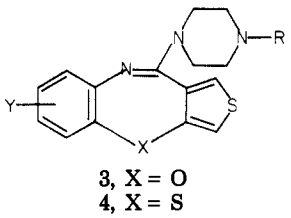
10-(Alkylamino)thieno[3,4-*b*][1,5]benzoxazepines (**3**) and 10-(alkylamino)thieno[3,4-*b*][1,5]benzothiazepines (**4**) were prepared by derivatization of the respective lactams (**7** and **8**) via phosphorus pentachloride and subsequent condensation with the appropriate alkylamines. 9-(Alkylamino)-4*H*-thieno[3,4-*b*][1,4]benzodiazepines (**5**) were prepared by titanium tetrachloride catalyzed condensation of the lactam **11** with alkylamines. 9-(Alkylamino)-4-methylthieno[3,4-*b*][1,4]benzodiazepines (**6**) were prepared by reductive alkylation of **5**. The compounds were tested for potential neuroleptic activity by means of the blockade of *d*-amphetamine lethality in aggregated mice and/or effects on locomotor activity in rats. Antidepressant activity was examined using inhibition of tetrabenazine-induced depression in mice. Most of the title compounds **3–6** were found to have neuroleptic activity. In addition, introduction of a 3-chloro substituent in the oxygen and sulfur systems (**3p** and **4c**), as well as introduction of an *N*-alkyl in the dinitrogen system (**6**), was found to produce antidepressant effects. Structure–activity relationships are discussed.

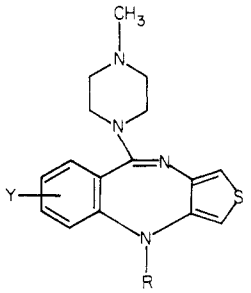
A previous report[2] from these laboratories discussed the synthesis and biological properties of 10-(alkylamino)-4*H*-thieno[3,4-*b*][1,5]benzodiazepines (**1** and **2**) as a novel class



1, R_1 = H
2, R_1 = alkyl



3, X = O
4, X = S

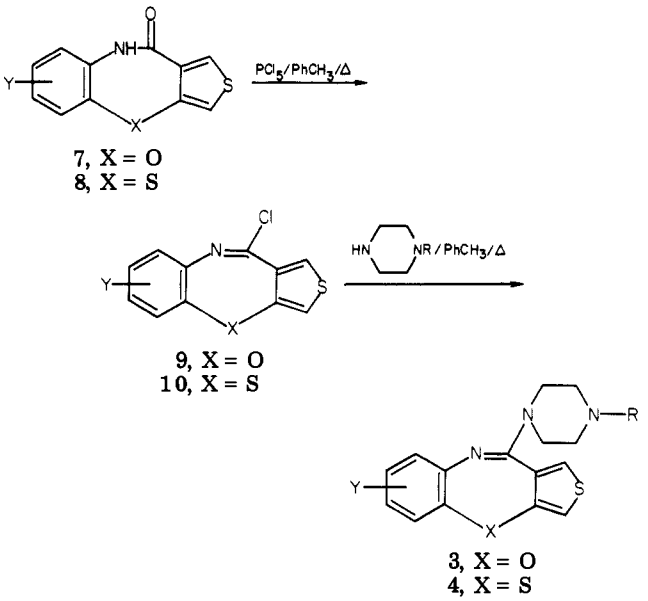


5, R = H
6, R = CH_3

of compounds with an interesting CNS profile. Encouraged by these results, we undertook further studies to prepare the 3,4-thieno analogues of loxapine[3] and clothiapine[3] (**3** and **4**), as well as other analogues of clozapine,[4] namely **5** and **6**, with the hope of discovering new CNS agents with improved therapeutic profiles or with mixed action effects as we reported for **2**.[2]

Chemistry. The appropriately substituted thieno[3,4-*b*][1,5]benzoxazepin-10-ones (**7**) and thieno[3,4-*b*]benzothiazepin-10-ones (**8**) were prepared by reaction of variously substituted 2-aminophenols or 2,2′-dithiobis(anilines) with 4-ethoxy-3-thiophenecarbonyl chloride, and subsequent ring closure of these intermediates was performed as described by us previously for the preparation of **7a** and **8a**.[5] The physical properties of the various lactams **7a–i** and **8a–d** are listed in Table IV.

Chart I. Preparation of Thieno[3,4-*b*][1,5]benzoxapines (**3**) and Thieno[3,4-*b*][1,5]benzothiazepines (**4**)



Conversion of lactams **7** and **8** to the biologically interesting title compounds **3** and **4** was accomplished as outlined in Chart I. The lactams were treated with a slight excess of phosphorus pentachloride in refluxing toluene to give imino chlorides **9** and **10**, respectively. The unpurified imino chlorides were immediately treated with an excess of the desired amine in toluene to give **3** and **4** as noncrystalline foams in moderate yields.[6a] These amidines were converted to their highly crystalline fumarate salts for characterization and biological testing. The physical properties of the various derivatives **3a–t** and **4a–e** are summarized in Table V.

The dinitrogen tricyclic lactam **11** was prepared as described in the previous paper.[1] As noted earlier for the isomeric thieno[3,4-*b*][1,5]benzodiazepine systems **1** and **2**,[2] attempts to derivatize **11** with phosphorus penta-

(1) For the previous paper in this series, see: Press, J. B.; Hofmann, C. M.; Safir, S. R. *J. Heterocycl. Chem.* **1980**, *17*, 1361.
(2) Press, J. B.; Hofmann, C. M.; Eudy, N. H.; Fanshawe, W. J.; Day, I. P.; Greenblatt, E. N.; Safir, S. R. *J. Med. Chem.* **1979**, *22*, 725.
(3) For a review of such dibenzoazepines, see: Schmutz, J. *Arzneim.-Forsch. (Drug. Res.)* **1975**, *25*, 712.
(4) (a) Gross, H.; Langner, E. *Arzneim.-Forsch. (Drug Res.)* **1969**, *19*, 496. (b) DeMaio, D. *Ibid.* **1972**, *22*, 919.
(5) Press, J. B.; Eudy, N. H.; Safir, S. R. *J. Org. Chem.* **1980**, *45*, 497.
(6) (a) These compounds are the subjects of U.S. Patent 4 157 444, 1979. (b) These compounds are the subjects of U.S. Patent 4 216 148, 1980.

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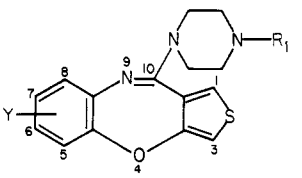
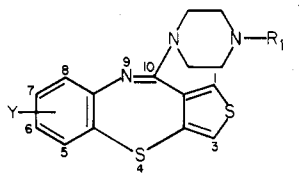
Table I. Biological Activity of Thieno[3,4-*b*][1,5]benzoxazepines (3)



no.	Y subst	R_1	GAL ED_{50},[a] mg/kg po	estimated motor act. MDD_{50},[b] mg/kg po	TBZ MED,[c] mg/kg po
3a	all H	CH_3	1.4 (1.0-2.0)	1.3	I[d]
3b	all H	CH_2CH_3	1.4 (1.1-1.9)	1.66	I
3c	all H	CH_2CH_2OH	≤10	5.4	I
3d	7-CH_3	CH_3	3.6 (2.4-5.6)	5.96	I
3e	7-CH_3	CH_2CH_3	3.9 (1.0-15.0)	<50	I
3f	7-CH_3	CH_2CH_2OH	I[e]	27.2	NT[f]
3g	6-CH_3	CH_3	I	NT	I
3h	6-CH_3	CH_2CH_2OH	NT	37	I
3i	8-CH_3	CH_3	1.2 (0.4-3.1)	>50	I
3j	8-CH_3	CH_2CH_2OH	I	NT	NT
3k	7-Cl	CH_3	1.6 (1.1-2.5)	9.6	I
3l	7-Cl	CH_2CH_3	6.8 (5.1-9.0)	≤50	I
3m	7-Cl	CH_2CH_2OH	2.0 (1.4-3.1)	19.2	I
3n	7-Br	CH_3	3.1 (2.5-3.9)	16.4	I
3o	7-Br	CH_2CH_2OH	<2.5	NT	I
3p	3-Cl	CH_3	2.4 (1.6-3.8)	<50	12.5
3q	3-Cl	CH_2CH_2OH	≤10	I[g]	I
3r	7-CH_3O	CH_3	I	NT	NT
3s	7-CH_3O	CH_2CH_2OH	I	NT	I
3t	6-CH_3O	CH_3	I	NT	I
loxapine			0.14 (0.09-0.24)	0.6	I
clozapine			4.2 (3.2-5.5)	21.0	I
imipramine			>50	>20	5[h]

[a] Protection vs. amphetamine lethality in grouped mice. [b] Dose causing 50% reduction of motor activity in rats. [c] Minimum effective dose causing antagonism of tetrabenazine (TBZ) induced depression in mice. [d] I = inactive at 25 mg/kg po for TBZ. [e] I = inactive at 20 mg/kg po for GAL. [f] NT = not tested. [g] I = inactive at 50 mg/kg ip for motor activity. [h] The MED for imipramine in TBZ was incorrectly given as 12 mg/kg in ref 2.

Table II. Biological Activity of Thieno[3,4-*b*][1,5]benzothiazepines (4)



no.	Y subst	R_1	GAL ED_{50},[a] mg/kg po	estimated motor act. MDD_{50},[b] mg/kg po	TBZ MED,[c] mg/kg po
4a	all H	CH_3	0.2 (0.1-0.6)	<10	I[d]
4b	all H	CH_2CH_2OH	0.2 (0.1-0.5)	≤10	I
4c	3-Cl	CH_3	I[e]	NT[f]	1.6
4d	7-Cl	CH_3	I	NT	I
4e	6,7-$(CH_3)_2$	CH_3	I	NT	I
loxapine			0.14 (0.09-0.24)	0.6	I
clozapine			4.2 (3.2-5.5)	21	I
imipramine			>50	>20	5[g]

[a] Protection vs. amphetamine lethality in grouped mice. [b] Dose causing 50% reduction of motor activity in rats. [c] Minimum effective dose causing antagonism of tetrabenazine (TBZ) induced depression in mice. [d] I = inactive at 25 mg/kg po for TBZ. [e] I = inactive at 20 mg/kg po for GAL. [f] NT = not tested. [g] The MED for imipramine in TBZ was incorrectly given as 12 mg/kg in ref 2.

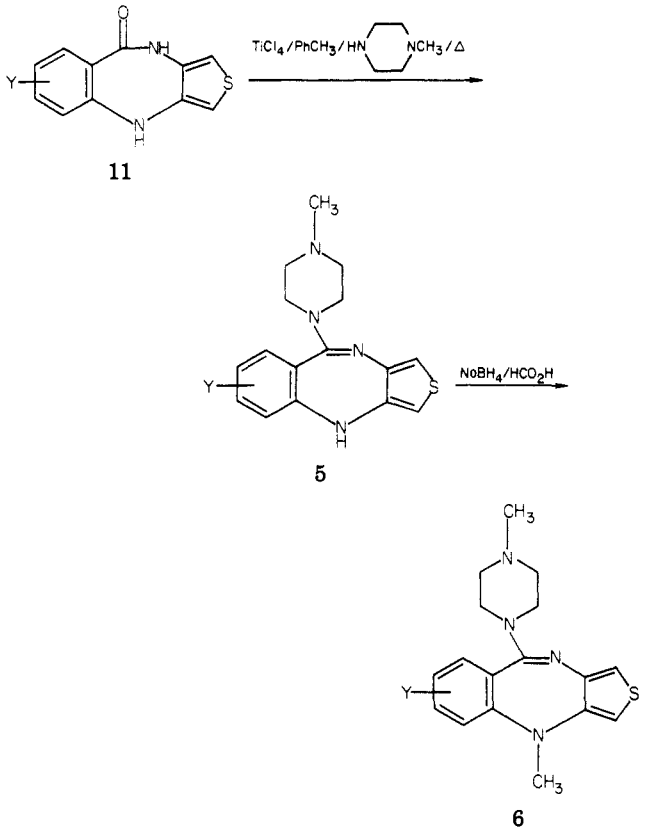
chloride caused extensive decomposition. The preparation of the desired title compounds **5** was accomplished by the procedure of Fryer et al.[7] and is outlined in Chart II.[6b] In this method, titanium tetrachloride catalyzed the direct condensation of amines with lactam **11**. The 4-(*N*-alkyl) derivatives **6** were prepared directly from **5** using a modified reductive alkylation procedure of Gribble.[8]

Pharmacology. The title compounds **3–6** were assessed for potential neuroleptic activity as measured by their antagonism of *d*-amphetamine-induced lethality in grouped mice (GAL) and/or their inhibition of motor ac-

(7) Fryer, R. I.; Early, J. V.; Field, G. F.; Fally, W.; Sternbach, L. H. *J. Org. Chem.* **1969**, *34*, 1143.

(8) Gribble, G. W. *Synthesis* **1975**, 650.

Chart II. Preparation of Thieno[3,4-*b*][1,4]benzodiazepines (5 and 6)



11 5 6

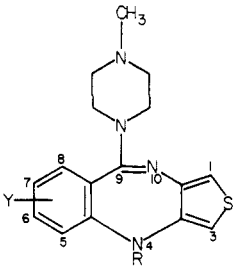
tivity in rats (MA). Such procedures are well documented to demonstrate the actions of neuroleptic drugs.[9] Antidepressant activity was measured by antagonism of tetrabenazine-induced depression of exploratory behavior in mice.[9a] Activities of the test compounds, as well as the reference agents loxapine, clozapine, and imipramine, are listed in Tables I–III. Several general observations concerning structure–activity relationships may be made from these data. Based on the structure–activity relationships observed previously,[2] only piperazine substitutions at C-10 were investigated. In the thieno[3,4-*b*][1,5]benzoxazepines (**3**), *N*-methyl- or *N*-ethylpiperazinyl substituents (**3a,b,d,e,g,i,k,l,n,p**) produce the most potent neuroleptic activity. As a consequence, our major efforts were directed toward *N*-alkylpiperazine derivatives for **4–6**.

More careful examination of the data for **3** (Table I) reveals that substitution of the aromatic nucleus at C-7 with methyl (**3d,e**), chlorine (**3k,l**), or bromine (**3n**) has little effect on neuroleptic activity compared to the all-hydrogen system (**3a,b**). Substitution at C-6 with methyl (**3g**) or at C-6 or C-7 with more electron-donating groups such as methoxy (**3r,t**) causes a complete loss of activity. Interestingly, chlorine substitution at C-3 (**3p**) maintains neuroleptic activity and confers potential antidepressant activity.

Comparison of thieno[3,4-*b*][1,5]benzoxazepines (**3**) with their sulfur analogues (**4**) indicates some surprising differences (Table II). The all-hydrogen system **4a** is an order of magnitude more potent as a neuroleptic agent (GAL) than its oxygen counterpart **3a** and is almost as potent as the reference agent loxapine. Secondly, the few samples of substitution examined (**4c–e**) show complete disappearance of activity and suggest an absence of a structure–activity correlation. Finally, as has been noted for

(9) (a) Greenblatt, E. N.; Lippa, A. S.; Osterberg, A. C. *Arch. Int. Pharmacodyn. Ther.* **1978**, *233*, 107. (b) Iverson, S. D.; Iverson, L. L. "Behavioral Pharmacology"; Oxford University Press: New York, 1975; pp 166. (c) Janssen, P. A. J.; Neimegeers, C. J. E.; Schellekens, K. H. L. *Arzneim.-Forsch.* **1965**, *15*, 104. (d) Burn, J. H.; Hobbs, R. *Arch. Int. Pharmacodyn. Ther.* **1958**, *113*, 290.

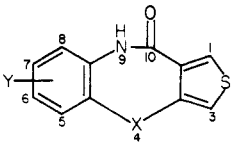
Table III. Biological Activity of 9-(4-Methyl-1-piperazinyl)-4*H*-thieno[3,4-*b*][1,4]-benzodiazepines (5 and 6)



no.	Y subst	R	GAL ED_{50},[a] mg/kg po	estimated motor act. MDD_{50},[b] mg/kg po	TBZ MED,[c] mg/kg po
5a	all H	H	3.2 (2.3–5.4)	15	I[d]
6a	all H	CH_3	6.5 (1.4–28)	51	7.6
5b	7-Cl	H	≤5.0	NT[e]	I
6b	7-Cl	CH_3	I[f]	4.1	1.56
5c	7-F	H	17.5 (9.0–33.0)	NT	I
6c	7-F	CH_3	I	NT	6.25
loxapine			0.14 (0.09–0.24)	0.6	I
clozapine			4.2 (3.2–5.5)	21	I
imipramine			>50	>20	5[g]

[a] Protection vs. amphetamine lethality in grouped mice. [b] Dose causing 50% reduction of motor activity in rats. [c] Minimum effective dose causing antagonism of tetrabenazine (TBZ) induced depression in mice. [d] I = inactive at 25 mg/kg po for TBZ. [e] NT = not tested. [f] I = inactive at 20 mg/kg po for GAL. [g] The MED for imipramine in TBZ was incorrectly given as 12 mg/kg in ref 2.

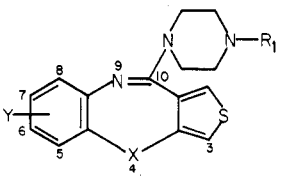
Table IV. Thieno[3,4-*b*][1,5]benzoxazepin-10-ones (7) and Thieno[3,4-*b*]benzothiazepin-10-ones (8)



no.	Y subst	X	% yield[a]	mp, °C	formula[b]
7a	all H[c]	O	68	239.5–241	$C_{11}H_7NO_2S$
7b	7-CH_3	O	48	209–213	$C_{12}H_9NO_2S$
7c	6-CH_3	O	84	209–216	$C_{12}H_9NO_2S$
7d	8-CH_3	O	21	194–195	$C_{12}H_9NO_2S$
7e	7-Cl	O	52	257–258	$C_{11}H_6ClNO_2S$
7f	7-Br	O	40	245–249	$C_{11}H_6BrNO_2S$
7g	3-Cl	O	64	258–260	$C_{11}H_6ClNO_2S$
7h	7-CH_3O	O	20	164–165	$C_{12}H_9NO_3S$
7i	6-CH_3O	O	33	243–244	$C_{12}H_9NO_3S$
8a	all H[c]	S	37	218–219	$C_{11}H_7NOS_2$
8b	3-Cl[c]	S	85	287–288	$C_{11}H_6ClNOS_2$
8c	7-Cl	S	35	267–269	$C_{11}H_6ClNOS_2$
8d	6,7-$(CH_3)_2$	S	15	264–265	$C_{13}H_{11}NOS_2$

[a] Percent yield represents yield for the ring closure of the synthetic sequence as outlined in ref 6. [b] All compounds gave satisfactory (±0.4%) combustion analyses. [c] See ref 5.

Table V. 4*H*-Thieno[3,4-*b*][1,5]benzoxazepines (3) and 4*H*-Thieno[3,4-*b*][1,5]benzothiazepines (4)



no.	Y subst	R_1	X	% yield[a]	mp, °C	formula[b]
3a	all H	CH_3	O	62; 36	217-220	$C_{16}H_{17}N_3OS \cdot C_4H_4O_4$[c]
3b	all H	CH_2CH_3	O	48; 36	215-217	$C_{17}H_{19}N_3OS \cdot C_4H_4O_4$
3c	all H	CH_2CH_2OH	O	74; 61	189-191	$C_{17}H_{19}N_3O_2S \cdot 0.5C_4H_4O_4 \cdot 0.25C_2H_5OH$
3d	7-CH_3	CH_3	O	70; 53	222-223	$C_{17}H_{19}N_3OS \cdot 0.5C_4H_4O_4$
3e	7-CH_3	CH_2CH_3	O	67; 58	208-209	$C_{18}H_{21}N_3OS \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$
3f	7-CH_3	CH_2CH_2OH	O	68; 48	178-180	$C_{18}H_{21}N_3O_2S \cdot 0.75C_4H_4O_4 \cdot 0.25\ H_2O$
3g	6-CH_3	CH_3	O	74; 16	215-216	$C_{17}H_{19}N_3OS \cdot C_4H_4O_4 \cdot 0.5C_2H_5OH$
3h	6-CH_3	CH_2CH_2OH	O	55; 21	198-200	$C_{18}H_{21}N_3O_2S \cdot 0.75C_4H_4O_4 \cdot 0.75H_2O$
3i	8-CH_3	CH_3	O	64; 57	160-161	$C_{17}H_{19}N_3OS \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$
3j	8-CH_3	CH_2CH_2OH	O	52; 36	182-183	$C_{18}H_{21}N_3O_2S \cdot 0.5C_4H_4O_4$
3k	7-Cl	CH_3	O	65; 42	180-182	$C_{16}H_{16}ClN_3OS \cdot 0.75C_4H_4O_4 \cdot 0.5C_2H_5OH$
3l	7-Cl	CH_2CH_3	O	33; 25	183-185	$C_{17}H_{18}ClN_3OS \cdot C_4H_4O_4$
3m	7-Cl	CH_2CH_2OH	O	59; 32	154-155	$C_{17}H_{18}ClN_3O_2S \cdot C_4H_4O_4$
3n	7-Br	CH_3	O	64; 51	196-197	$C_{16}H_{16}BrN_3OS \cdot 0.25C_4H_4O_4 \cdot 0.5H_2O$
3o	7-Br	CH_2CH_2OH	O	40; 14	150-152	$C_{17}H_{18}BrN_3O_2S \cdot 0.5C_4H_4O_4$
3p	3-Cl	CH_3	O	72; 70	170-172	$C_{16}H_{16}ClN_3OS \cdot C_4H_4O_4$
3q	3-Cl	CH_2CH_2OH	O	36; 25	144-145	$C_{17}H_{18}ClN_3O_2S \cdot C_4H_4O_4$
3r	7-OCH_3	CH_3	O	50; 23	206-208	$C_{17}H_{19}N_3O_2S \cdot C_4H_4O_4$
3s	7-OCH_3	CH_2CH_2OH	O	57; 20	149-150	$C_{18}H_{21}N_3O_3S \cdot C_4H_4O_4$
3t	6-OCH_3	CH_3	O	57; 14	188-189	$C_{17}H_{19}N_3O_2S \cdot 0.5C_4H_4O_4$
4a	all H	CH_3	S	69; 48	186-188	$C_{16}H_{17}N_3S_2 \cdot C_4H_4O_4$
4b	all H	CH_2CH_2OH	S	70; 50	189.5-190	$C_{17}H_{19}N_3OS_2 \cdot 0.5C_4H_4O_4$
4c	3-Cl	CH_3	S	70; 50	163-165	$C_{16}H_{16}ClN_3S_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$
4d	7-Cl	CH_3	S	73; 72	234-235	$C_{16}H_{16}ClN_3S_2 \cdot C_4H_4O_4$
4e	6,7-$(CH_3)_2$	CH_3	S	66; 22	205-207	$C_{18}H_{21}N_3S_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$

[a] Percent yield: first value is yield of free base, second value is yield of the salt. See Experimental Section. [b] All compounds gave satisfactory (±0.4%) combustion analyses. [c] $C_4H_4O_4$ = fumarate.

the oxygen system (**3p**) and the thieno[3,4-*b*][1,5]benzodiazepine system **2**,[2] chlorine substitution at C-3 (**4c**) leads to potential antidepressant activity (TBZ); however, neuroleptic activity disappears in this case.

Finally, examination of the biological data for thieno[3,4-*b*][1,4]benzodiazepines (**5** and **6**) and comparison to oxygen system **3**, sulfur system **4**, and isomeric [1,5] systems (**1** and **2**),[2] reveal the now expected properties (Table III). As noted for **1** and **2**,[2] 4-alkyl substitution of **5** yields products (**6**) having antidepressant activity. Both **5** and **6** were relatively less potent both in GAL and TBZ than their [1,5] counterparts **1** and **2**[2] and in GAL as compared to **3** and **4**.

While these novel tricyclic systems (**3–6**) are interesting as potential neuroleptic and/or antidepressant agents, they do not meet our initial objectives. Thieno[3,4-*b*][1,5]-benzoxazepines (**3**) and thieno[3,4-*b*][1,5]benzothiazepines (**4**) show neuroleptic activity but little interesting antidepressant activity. Thieno[3,4-*b*][1,4]benzodiazepines (**5**) also display neuroleptic activity but show no advantage over their [1,5] isomers **1**.[2] Thieno[3,4-*b*][1,4]benzodiazepines (**6**) have the neuroleptic/antidepressant mixed action profile similar to their previously reported [1,5] isomers **2**,[2] but **6** are less potent than **2** and thus offer no apparent advantage. Among the most interesting results of our study was that chlorination at C-3 of systems **3** and **4** (namely, **3p** and **4c**) conferred antidepressant properties in systems that primarily behave as neuroleptic agents. Introduction of a mixed action CNS profile by means of simple substitutional changes may be a subject of interest for future studies.

Experimental Section

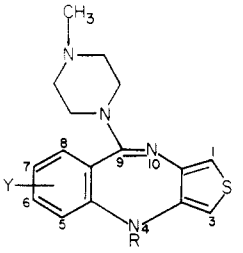
Melting points were determined on a Mel-Temp capillary block melting point apparatus and are uncorrected. All compounds are homogeneous by thin-layer chromatographic analysis using Whatman K5F (5 × 10 cm) silica gel analytical plates. ^1H NMR measurements were made on a Varian Associates HA-100A spectrometer, and shift values are reported downfield from tetramethyl silane as the internal standard. Mass spectral measurements were made on a AEI MS-9 mass spectrometer. The procedures reported herein represent general synthetic operations used for preparation of the compounds in Tables IV–VI.

Substituted Thieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-ones (7; Table IV). The appropriately substituted 2-aminophenol (0.05 mol) in methylene chloride (100 mL) containing triethylamine (5.05 g, 0.05 mol) was treated with a solution of 4-ethoxy-3-thiophenecarbonyl chloride (9.52 g, 0.05 mol) dropwise in the manner described.[5] The product was collected by filtration, washed with water, dried, and isolated in 43–93% yield. This material was then treated with polyphosphoric acid (100 g/5 g of reactant) at 120 °C for 1–2 h as described.[5] The lactams **7** were isolated by dilution of the reaction mixture with water and filtration to collect the solid. Physical properties of **7** are summarized in Table IV.

Substituted Thieno[3,4-*b*][1,5]benzothiazepin-10(9*H*)-ones (8; Table IV). The appropriately substituted 2,2′-dithiobis(4-ethoxythiophene-3-carboxanilide) was prepared in 50–70% yield in a manner similar to the above by reaction of 2,2′-dithiobis(aniline) and 4-ethoxy-3-thiophenecarbonyl chloride and was described in detail previously.[5] The thus obtained disulfides were reduced to the mercaptans with excess sodium borohydride in methanol as described.[5] Lactams **8** were prepared by ring closure of the above mercaptan in polyphosphoric acid at 120 °C and isolated using silica gel column chromatography.[5] The physical properties of **8** are summarized in Table IV.

10-(4-Methyl-1-piperazinyl)thieno[3,4-*b*][1,5]benzoxazepine Fumarate (3a; Table V). A mixture of 2.17 g (0.01 mol) of thieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-one,[5] 2.28 g (0.011 mol) of phosphorus pentachloride, and 50 mL of dry toluene was refluxed for 4 h. The reaction was concentrated to a thick oil, triturated 2 times with toluene, and reconcentrated. To this imino chloride was added 10 mL of dry toluene and 10 mL (0.09 mol)

Table VI. 9-(4-Methyl-1-piperazinyl)-4*H*-thieno[3,4-*b*][1,4]benzodiazepines (5 and 6)



no.	Y subst	R	% yield	mp, °C	formula[a]
6a	all H	CH_3	60	206–208 dec	$C_{17}H_{20}N_4S \cdot C_4H_4O_4 \cdot 0.5H_2O$[b]
5a	all H	H	76	177–180	$C_{16}H_{18}N_4S$
5b	7-Cl	H	14.5	191–194 dec	$C_{16}H_{17}ClN_4S$[c]
6b	7-Cl	CH_3	61	227–230 dec	$C_{17}H_{19}ClN_4S \cdot C_4H_4O_4$
5c	7-F	H	59	224–227 dec	$C_{16}H_{17}FN_4S$
6c	7-F	CH_3	68	189–195 dec	$C_{17}H_{19}FN_4S \cdot 0.75C_4H_4O_4 \cdot H_2O$

[a] All compounds gave (±0.4%) combustion analyses except where noted. [b] $C_4H_4O_4$ = fumarate. [c] N: calcd, 16.83; found, 16.30. Cl: calcd, 10.65; found, 11.19.

of *N*-methylpiperazine, and the mixture was refluxed with stirring for 18 h. The reaction mixture was cooled and concentrated, and the residue was dissolved in 200 mL of 2 N acetic acid. The solution was filtered, cooled, made basic with concentrated ammonium hydroxide, and extracted with methylene chloride. The organic layer was washed with water, dried over potassium carbonate, and concentrated. The resulting oil was dissolved in the appropriate amount of methylene chloride and filtered through magnesium silicate. The product (1.85 g, 62%) could not be crystallized; 1.50 g (0.005 mol) of this oily base was dissolved in 25 mL of hot ethanol, filtered, and concentrated to 15 mL. To this was added a filtered solution of 0.58 g (0.005 mol) of fumaric acid in 20 mL hot ethanol. The product crystallized to give 1.20 g (58%) of white microcrystals: mp 217–220 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.60 (d, 1 H), 7.13 (d, 1 H, both thiophene H) 7.02 (m, 4 H, aromatic H), 6.62 (s, 2 H, fumarate H), 3.62, 2.58 (m, 4 H each, CH_2N), 2.34 (s, 3 H, NCH_3).

10-(4-Ethyl-1-piperazinyl)thieno[3,4-*b*][1,5]benzoxazepine Fumarate (3b; Table V). Thieno[3,4-*b*][1,5]benzoxazepin-10-(9*H*)-one[5] (1.08 g, 0.005 mol) was converted to imino chloride **9** with phosphorus pentachloride (1.15 g, 0.005 mol) as described above. To the crude imino chloride was added 10 mL of dry toluene, 1.2 g (0.01 mol) of *N*-ethylpiperazine, and 2.5 mL (0.018 mol) of triethylamine, and the whole was refluxed for 18 h. The workup of the free base is the same as that described above. The product (0.750 g, 48%) was converted to the fumarate to give 0.780 g (76%) of white needles: mp 215–217 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.65 (d, 1 H), 7.17 (d, 1 H, both thiophene H), 7.02 (m, 4 H, aromatic H), 6.58 (s, 2 H, fumarate H), 3.60 (m, 4 H, CH_2N), 2.65 (m, 6 H, CH_2N), 1.06 (t, 3 H, CH_3).

4-(Thieno[3,4-*b*][1,5]benzoxazepin-10-yl)-1-piperazineethanol Hemifumarate (3c; Table V). The imino chloride was prepared as above by the action of phosphorus pentachloride (1.14 g, 0.0259 mol) on thieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-one[5] (5.10 g, 0.0235 mol). To the crude imino chloride was added 20 mL dry toluene and 20 mL of dry *N*-(hydroxyethyl)piperazine, and the mixture was refluxed with stirring for 18 h. After workup as described above, the product was isolated as off-white crystals (4.98 g, 75%), mp 103–105 °C.

This free base (3.42 g, 0.0104 mol) was dissolved in 50 mL of hot ethanol and filtered. To this was added a solution of 1.19 g (0.0104 mol) of fumaric acid in 50 mL of hot ethanol. The product crystallized to give 2.84 g (61%) of off-white crystals. The analytical sample was recrystallized from hot ethanol to give white crystals: mp 189–191 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.64 (d, 1 H), 7.18 (d, 1 H, both thiophene H), 7.00 (m, 4 H, aromatic H), 6.58 (s, 1 H, fumarate H), 3.57 (m, 6 H, CH_2N, CH_2O), 3.40 (m, 6 H, CH_2N).

Frequently, the fumarate salts crystallized as solvates. Several attempts to completely remove solvent from the crystals (heat/vacuum) caused loss of crystallinity.

Occasionally, variations on the general procedure were required, such as (1) redissolving the free base in 2 N acetic acid and reprecipitating with concentrated ammonium hydroxide prior to preparation of the fumarate or (2) filtering the methylene chloride solution of the free base through magnesium silicate a second time prior to salt formation.

On one occasion [4-(7-bromothieno[3,4-*b*][1,5]benzoxazepin-10-yl)-1-piperazineethanol fumarate (**3o**)], sublimation of the free base was required prior to salt formation.

10-(4-Methyl-1-piperazinyl)thieno[3,4-*b*][1,5]benzothiazepine Fumarate (4a; Table V). Thieno[3,4-*b*][1,5]-benzothiazepin-10(9*H*)-one[5] (0.58 g, 0.0025 mol) was converted as above to imino chloride **10** with phosphorus pentachloride (0.63 g, 0.003 mol). The resultant product was reacted with *N*-methylpiperazine (2 mL) in refluxing toluene (10 mL) overnight. Workup as before gave the amidine as a yellow foam, 0.54 g (69%). Reaction of fumaric acid (0.195 g, 0.00168 mol) in hot ethanol (20 mL) with the amidine gave the fumarate salt, which was crystallized from ethanol–ether: yield 0.35 g (48%); mp 186–188 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.66 (d, 1 H), 7.53 (d, 1 H, both thiophene H), 7.2 (m, 2 H), 6.9 (m, 2 H, all aromatic H), 6.57 (s, 2 H, fumarate H), 3.56 (m, 4 H, CH_2), 2.53 (m, 4 H, CH_2), 2.32 (s, 3 H, CH_3).

9-(4-Methyl-1-piperazinyl)-4*H*-thieno[3,4-*b*][1,4]benzodiazepine Fumarate (5a; Table VI). The procedure used is the Schneider[10] modification of the Fryer[7] method. To a mechanically stirred mixture of 40 mL of dry toluene, 4 mL of anisole, and 2.4 mL (0.025 mol) of titanium tetrachloride there was added 0.09 mol of *N*-methylpiperazine (or piperazine) and 10 mL of toluene. To this complex were added 0.02 mol of the 4*H*-thieno[3,4-*b*][1,4]benzodiazepin-9(10*H*)-one[1] and 0.054 mol of *N*-methylpiperazine in 20 mL of toluene, and the resulting solution was refluxed for 3.5 h.

The reaction mixture was cooled to 60 °C and 7 mL of isopropyl alcohol was added, followed by 4 g of diatomaceous earth and 5 mL of concentrated ammonium hydroxide. The refluxing mixture was filtered and the solid cake was washed extensively with toluene. The organic layer was extracted with 3 N hydrochloric acid and the product precipitated with ammonium hydroxide. The solid was collected, dissolved in methylene chloride, and the organic phase was filtered through magnesium silicate. The filtrate was evaporated to give the **5a** as a solid, which was recrystallized from a mixture of methylene chloride and hexanes. The solid was dissolved in alcohol and treated with a warm alcoholic solution of fumaric acid. The fumarate precipitated and was recrystallized from alcohol: ^{1}H NMR δ 7.50 (s, 1 H, NH), 7.08 (ab quartet, 4 H, aromatic H), 6.54 (m, 2 H, thiophene H), 3.26 (m, 4 H, CH_2N), 2.50 (m, 4 H, CH_2N), 2.28 (s, 3 H, NCH_3).

4-Methyl-9-(4-methyl-1-piperazinyl)-4*H*-thieno[3,4-*b*][1,4]benzodiazepines Fumarates (6a; Table VI). The method used to prepare these compounds is a modified Gribble procedure.[8] A mixture of 0.01 mol of the 9-(4-methyl-1-piperazinyl)-4*H*-thieno[3,4-*b*][1,4]benzodiazepine (**5a**) and 35 mL of 97% formic

(10) Schneider, J. German Offenlegungsschrift 2316438, 1974.

acid was stirred and cooled as 3.8 g (0.1 mol) of sodium borohydride pellets was added over 0.5 h. The mixture was stirred at room temperature for several hours, during which time additional pellets of sodium borohydride were added. Stirring was continued until no more starting material was present by TLC.

The mixture was cooled, diluted with water, made alkaline with NH_4OH, and extracted several times with methylene chloride. The extracts were dried ($MgSO_4$) and filtered, and the filtrate was evaporated to give the product as a glass. The glass was dissolved in alcohol and treated with an alcoholic solution of fumaric acid. The fumarate precipitated and was recrystallized from alcohol: ^1H NMR (Me_2SO-d_6) δ 7.11 (m, 4 H, aromatic H), 6.56 (m, 4 H, thiophene H and fumarate H), 3.28 (m, 4 H, CH_2N), 3.08 (s, 3 H, aromatic NCH_3), 2.58 (m, 4 H, CH_2N), 2.28 (s, 3 H, NCH_3).

Pharmacological Testing Methods. Antagonism of *d*-amphetamine lethality in grouped mice was determined using a previously reported procedure.[9] Groups of 10 mice were treated with the test compound at graded doses and placed in wire mesh cages (20 × 13 × 13.5 cm) in a controlled temperature room at 22 ± 2 °C. After 30 min, *d*-amphetamine sulfate in saline was administered at a dose of 15 mg/kg, which caused 90–100% deaths in untreated grouped mice. Deaths were measured after 24 h. ED_{50} values were determined and defined as the dose of compound that prevented death in 50% of the test animals.

Effects of the compounds on locomotor activity in rats were determined as previously described[9] by oral treatment of groups of five rats with graded doses of the test compounds. Locomotor activity was determined for each individual rat as measured over a 5-min interval at the time of peak effect (previously measured using a selected dose of the compound) utilizing an Animex activity counter. The MDD_{50} was measured from a linear-regression analysis and is defined as the dose that produces 50% reduction in motor activity as compared to the control animals.

Inhibition of tetrabenazine-induced depression of exploratory behavior in mice was determined in the reported manner.[9] Groups of five mice were treated with a dose of the test compound orally and after 1 h were treated with tetrabenazine hexamate (aqueous) at a dose of 30 mg/kg ip. Treated mice were placed on a horizontal disk (18-in. diameter) after 30 min and exploratory behavior was measured within 10 s according to an observational response rating scale. The MED (minimum effective dose) was established by dosing initially at 25 mg/kg orally and halving the dose until the test compound is found inactive in the above procedure.

Synthesis and Antiarrhythmic Activity of New Benzofuran Derivatives

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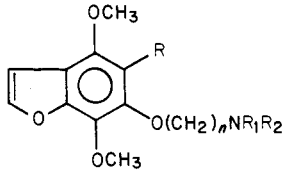
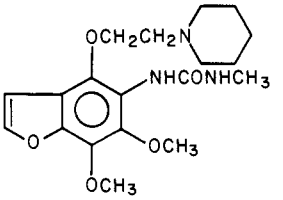
Various 5-aminobenzofuran derivatives were prepared from khellin and screened intravenously in the dog for their potential antiarrhythmic activity against ouabain-induced ventricular arrhythmia and in the Harris test. From systematic structural variations it was found that two methoxy groups in positions 4 and 7 on the benzofuran ring, a tertiary aminoethoxy side chain in position 6, and a *N*-methylurea group in position 5 led to the most active compounds. These were then tested orally in the Harris test in the dog. The two long-acting derivatives *N*-[4,7-dimethoxy-6-(2-pyrrolidinoethoxy)-5-benzofuranyl]-*N'*-methylurea (**8j**) and *N*-[4,7-dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]-*N'*-methylurea (**8m**) showed advantages when compared to quinidine and disopyramide and have been selected for further studies.

The benzofuran ring system is the basic skeleton of numerous compounds possessing cardiovascular activities.[1] In a sustained effort to find cardiovascular active agents derived from khellin,[2-4] a series of *N*-[[6-[alkyl(and dialkyl)amino]alkoxy]-4,7-dimethoxy-5-benzofuranyl] derivatives was prepared and screened for its potential activity.

Several of the compounds typified by **1** exhibited a marked antiarrhythmic activity, as shown by their antagonism to ouabain-induced ventricular arrhythmia in the dog.[5] Since these compounds were not active enough against ventricular arrhythmia induced by Harris coronary ligation,[6] synthesis was extended to compounds **2–13**. Derivatives **8** were the most potent in both tests previously quoted. The results of this study suggested further modifications, which led to the synthesis of compounds **14–16d** (see Table I) and **17–19**. Synthesis and structure–activity relationships are described herein.



1, R = $NHCOCH_3$
2, R = NH_2
3, R = $NHCH_3$
4, R = NHCHO
5, R = NHCO-alkyl
6, R = NHCOO-alkyl
7, R = $NHCONH_2$
8, R = $NHCONHCH_3$
9, R = NHCONH-alkyl
10, R = $NHSO_2NHCH_3$
11, R = $NHCSNHCH_3$
12, R = $NHCON(CH_3)_2$
13, R = $N(CH_3CONHCH_3$



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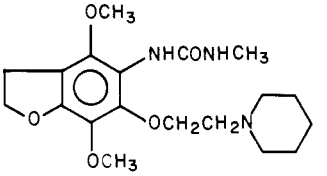

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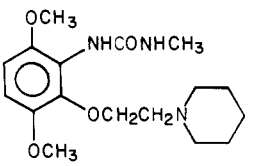

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